Research priorities in bronchiectasis

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Title

Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration

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Take home message

An EMBARC consensus statement identifies research priorities in bronchiectasis as determined by physicians and patients.

ABSTRACT

Bronchiectasis is a disease of renewed interest in light of an increase in prevalence and increasing burden on international healthcare systems. There are no licensed therapies and large gaps in knowledge in terms of epidemiology, pathophysiology and therapy. The European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) is a European Respiratory Society Clinical Research Collaboration, funded by ERS to promote high quality research in bronchiectasis. The objective of this consensus statement was to define research priorities in bronchiectasis. From 2014-2015 EMBARC used a modified Delphi process among European bronchiectasis experts to reach a consensus on 55 key research priorities in this field. During the same period, the European Lung Foundation collected 711 questionnaires from adult patients with bronchiectasis and their carers from 22 European countries reporting important research priorities from their perspective. This consensus statement reports recommendations for bronchiectasis research after integrating both physicians and patients priorities, as well as those uniquely identified by the two groups. Priorities identified in this consensus statement provide the clearest possible roadmap towards improving our understanding of the disease and the quality of care for patients with bronchiectasis.

SUMMARY OF RECOMMENDATIONS

1. DNA biobanks linked to well phenotyped patient cohorts should be established to enable underlying genetic susceptibility to bronchiectasis to be established.
2. Observational research in large patient cohorts is needed to establish the natural history of bronchiectasis due to different aetiologies.
3. A comprehensive study enrolling patients when stable and during exacerbation should be conducted, evaluating the impact of bacteria, viruses, fungi and non-infectious stimuli to identify the cause(s) of bronchiectasis exacerbations.
4. Studies are required to optimize compliance and access to chest physiotherapy and pulmonary rehabilitation in bronchiectasis.
5. A deeper understanding of the inflammatory pathways in bronchiectasis is needed to develop new therapies. We recommend using emerging techniques and technologies (particularly proteomics, metabolomics and genomics) in large well-characterized cohorts to identify new treatment targets and deeper patient phenotyping.
6. An implementation study should be performed to demonstrate if the use of bronchiectasis severity scores could improve patient care.
7. A randomized controlled trial of *Pseudomonas aeruginosa* eradication therapy, compared to no eradication treatment, should be performed.
8. A randomized controlled trial comparing at least 14 days of antibiotic treatment for exacerbations with shorter course treatments is required.
9. We suggest studies of the microbiome (incorporating bacteria and potentially fungi) in bronchiectasis linked to detailed clinical phenotyping data.

10. A longitudinal study of the bacteriology of bronchiectasis incorporating data on antibiotic resistance is needed.
11. Longitudinal studies should be conducted in patients receiving oral and inhaled antibiotics to monitor for the emergence of antibiotic resistance.
12. Studies should ideally evaluate whether cyclical or continuous administration of long-term antibiotics is superior both in terms of clinical efficacy and the emergence of resistance.
13. Further studies are required to define the optimal patient population to benefit from long-term macrolide therapy.
14. More “real world” data on the long-term safety and resistance impact of macrolide treatment are required.
15. Inhaled antibiotics such as colistin and gentamicin should be subject to definitive phase III trials to demonstrate a reduction in exacerbations and improvements in quality of life.
16. Mechanistic studies investigating the genetic, microbiological, inflammatory and clinical susceptibility factors for *P. aeruginosa* colonization should be conducted.
17. Long-term cohort studies are needed to identify which patients acquire *P. aeruginosa* colonization and to identify its independent effects on outcome.
18. Comparative studies are needed to determine the optimal choice between oral and inhaled antibiotic treatment in patients with and without *P. aeruginosa* colonization.
19. Randomized controlled trials should address whether alternative long-term oral antibiotics (other than macrolides) are effective at reducing exacerbations.
20. Studies should be conducted to determine the effectiveness of patient self-management in bronchiectasis and adherence to treatment.

21. Further research with patients as partners could explore the specific information needs of bronchiectasis patients, effective health care professionals and patient communication strategies, and develop improved patient-reported outcomes.
22. A multidisciplinary education programme is needed for bronchiectasis to increase awareness among non-specialists in secondary care and among primary care.

INTRODUCTION

Bronchiectasis is a chronic lung disorder characterized by permanent dilatation of bronchi leading to impaired mucociliary clearance, chronic airway inflammation and bacterial colonization [1]. Although historically considered a neglected disease, bronchiectasis has become a disease of renewed interest over the past decades in light of an increase in prevalence and an increasing burden on healthcare systems [2-8]. To date, treatment of bronchiectasis is mainly extrapolated from cystic fibrosis (CF) and COPD, or based on expert opinions as high quality evidence is still missing [9]. Large gaps in our knowledge could be identified on several aspects of this disease and this emphasizes the need for additional clinical and translational research, as well as collaborative working.

Towards these goals, the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) was developed in 2012 as the first international bronchiectasis network, seeking to promote clinical and translational research in bronchiectasis (www.bronchiectasis.eu)[10]. Since 2014, the EMBARC network also represents an official European Respiratory Society (ERS) Clinical Research Collaboration (CRC), as group of researchers approved and funded by this society to promote collaboration and research excellence in Europe and beyond. With this ERS support, has come the additional benefit of patient involvement facilitated by the European Lung Foundation (ELF; www.europeanlung.org). ELF was founded in 2000 with the aim of bringing together patients and the public with respiratory professionals to positively influence lung health. One way that this is achieved is by involving patients in identifying patient-centred outcomes and a focus on quality of life integrated into the EMBARC and CRC activities [11].

The first challenge the EMBARC collaborative group has recognized was to reach a consensus on the main clinical and translational research priorities in the field of bronchiectasis. We used a modified Delphi process among European bronchiectasis experts alongside a questionnaire of European patients with bronchiectasis and carers to identify the major clinical and research priorities in this disease. Here we present a consensus statement of the EMBARC CRC based on the findings of these survey approaches.

METHODS

Two parallel processes were performed: a modified Delphi process involving European physicians caring for patients with bronchiectasis and a questionnaire process to survey the perspectives of patients with bronchiectasis and carers, see Figure 1.

Experts research priorities

From July 2014 to November 2014, a working group composed by eight EMBARC members from 5 European countries was established. The objective of this group was to systematically evaluate the available literature and to produce a consensus on the most important research questions in the field of bronchiectasis. The working group was asked to draft the most important research questions on bronchiectasis split into 10 separate sections: epidemiology; pathogenesis and mechanisms of the disease; aetiology, radiology and physiology; microbiology and microbial diagnostics; acute and long-term suppressive antibiotic therapy; non antibiotic and anti-inflammatory therapies; physiotherapy and pulmonary rehabilitation; outcomes, prognosis and healthcare utilization; exacerbation and others. A Delphi approach was then used to reach a consensus (agreement >85%) on the most important research questions in the field [12]. All the process was carried out anonymously. From December 2014 to February 2015, the list of research priorities agreed by the working group was sent electronically to 138 EMBARC members representing 23 European countries who were asked to grade anonymously each research question using a 5-level scale (from unimportant to essential).

Patient and carer research priorities

During the same period a questionnaire to look into the research priorities of patients and carers was developed. The aim was to identify the challenges of treating and living with bronchiectasis from the perspectives of people with bronchiectasis, their families and friends and to prioritize what they think needs to change or be considered to have the greatest impact on quality of life for people with bronchiectasis. The questionnaire was developed by members of the EMBARC Roadmap Study Group (S.A., J.D.C. and E.P.) and ELF (S.M. and P.P.), reviewed by an advisory group of four "expert patients" with bronchiectasis, and revised to ensure that it met the needs of the project and would be relevant, interesting and accessible for patients and carers (see online supplement). Furthermore, the items in the questionnaire were broadly aligned with the ten research sections identified by the experts to be covered in the roadmap so that the relative significance for patients and professionals could be compared. Expert questions were translated into language accessible for patients by the advisory group, and in some cases expert questions were discarded or replaced. The respondents were asked to rate anonymously what aspect of their or their relative/friend's bronchiectasis is found the most difficult to manage. For each aspect listed, they could have selected 'not an issue', 'not very difficult', 'difficult', 'very difficult', or 'no opinion'. Respondents were also asked to prioritise questions according to four areas of research (bronchiectasis management by doctors; treatment; monitoring; self-management by patients) selecting 'unimportant', 'not very important', 'important', 'very important' or 'no opinion' for each of them. The questionnaire was published online and an invitation was sent to patients with bronchiectasis all over Europe via ERS, ELF and EMBARC patient and healthcare professional (HCP) networks/clinics. The questionnaire was available online from December 2014 to April 2015, in 12 languages (English, German, French, Dutch, Spanish,

Italian, Portuguese, Greek, Russian, Polish, Turkish and Arabic). The questionnaire was also available in a printable format for healthcare professionals to provide to their patients with a paper copy, with the responses input online anonymously by a member of administrative staff at the HCP's clinic. Ethical approval was waived for the active involvement of patients as either advisors or participants in questionnaires, see online supplement.

Consensus statements

Following review of the highest scoring research priorities across both physician and patient survey exercises, the EMBARC roadmap working group have produced a series of agreed consensus statements on research priorities in bronchiectasis.

RESULTS

Experts' research priorities

A total of 365 potential research questions were initially drafted by the EMBARC Roadmap Study Group and after a check for repetitions, discrepancy or inconsistency a shortlist of 150 research questions was defined. The modified Delphi process then involved several rounds of revision, in which the study group agreed with, disagreed with or suggested changes to the 150 research questions that they and the other participants had proposed. The responses were collated and sent back to participants who were then able to revise their judgment in light of the group feedback. This process was repeated three times. Response from the members of the EMBARC Roadmap Study Group was 100% during each of the three rounds. At the end of the Delphi process a final consensus (>85% agreement) was reached on 55 research questions. To determine which of these research questions had the greatest priority, the 55 research questions were then sent electronically to 138 EMBARC members representing 23 European countries. One hundred EMBARC members graded the list of research questions (response rate was 72%). The final list of the experts' research priorities after grading is shown in Table 1.

Patients' research priorities

A total of 1,086 questionnaires were completed. Of these, 711 were considered for analysis, meeting the following criteria: age, gender, resident in geographical Europe, and either a person with bronchiectasis, a parent, relative, carer or friend of someone with bronchiectasis. The respondents covered 22 countries (UK, Germany, Turkey, Spain, France, Italy, Portugal, Netherlands, Russia, Ireland, Belgium, Norway, Greece, Switzerland, Poland,

Hungary, Bulgaria, Romania, Austria, Sweden, Finland, Luxemburg), see Figure A in the online supplement. The dominant characteristics of respondents were: 87% patients; 71% female; and aged 31-50 (30%) or 61-70 (27%) years, see Figures B and C in the online supplement.

The aspects of bronchiectasis that patients considered the most difficult to manage are reported in Figure 2a. Every aspect listed was found difficult by more than 23% of respondents. However, despite all aspects being found difficult or very difficult by some, seven of the aspects were also identified as not an issue for between 21 and 53% of respondents, see Figure 2b. Thus, each person's experience of their bronchiectasis and the aspects that they find most difficult to manage varies.

Patient's research priorities are reported in Figures D-G in the online supplement, according to the four research areas (bronchiectasis management by doctors; treatment; monitoring; self-management by patients), while Table 2 shows the 29 research priorities across all the four areas. In addition, 42% of respondents outlined other important topics for research, with the most common additional themes being infection and the immune system, mental health and quality of life, nutrition and exercise, and managing mucus/phlegm.

The key research priorities are now briefly discussed in the following sections: 1) Research priorities commonly identified by both experts and patients; 2) Important research priorities identified by experts; 3) Important research priorities identified by patients. The full version of the discussion of research priorities is reported in the online supplement.

DISCUSSION

Research priorities commonly identified by both experts and patients

1. What are the causes of bronchiectasis? (Patients) / What are the baseline investigations to evaluate etiologies in patients with bronchiectasis? (Experts)

One of the cornerstones in the management of bronchiectasis is the identification and treatment of underlying causes. Several predisposing factors might be identified including previous severe respiratory infections, allergic bronchopulmonary aspergillosis, impairment of ciliary clearance, primary or secondary immunodeficiency, and other diseases associated to bronchiectasis, such COPD and severe asthma. Despite following guidelines recommendations, an etiology of bronchiectasis cannot be reached in 40% of the patients, whilst an etiology of bronchiectasis leading to a change in patient's management may be identified in only 13% of the cases [13]. Further research should integrate basic research from the "-omics" perspective with clinical data in order to identify the possible etiologies among the large group of patients with idiopathic bronchiectasis.

Consensus statements: 1) DNA biobanks linked to well phenotyped patient cohorts should be established to enable underlying genetic susceptibility to bronchiectasis to be established; 2) Observational research in large patient cohorts is needed to establish the natural history of bronchiectasis due to different aetiologies.

2. What are the triggers of an exacerbation? (Patients) / What are the causes of an exacerbation of bronchiectasis? (Experts)

From an infective point of view, changes in airway bacterial community composition, emergence of new strains, as well as spread of infection by the same species to new regions of the lung might trigger exacerbations [14-16]. New airway infection caused by organisms present in low abundance (and thus that may be not detected with conventional techniques) yet identifiable by metagenomic approaches could help us in understanding what is responsible for triggering a new exacerbation [17]. It could be also possible that exacerbations may be driven by changes and/or adaptation in strains that cannot be detected by such approaches and hence metabolomics techniques may help. The role of viruses in triggering infective exacerbations should also be better defined [18], as well as their interaction with bacteria in both stable state and during exacerbations. Finally, the "vicious-cycle" hypothesis that characterized the physiopathology of bronchiectasis patients in stable state does not rule out the possibility that non-infectious triggers, including indoor and outdoor air pollution, might cause exacerbations and further prospective observational studies are needed in this area [19].

Consensus statement: A comprehensive study enrolling patients when stable and during exacerbation should be conducted, evaluating the impact of bacteria, viruses, fungi and non-infectious stimuli to identify the cause(s) of bronchiectasis exacerbations.

3*. How can we improve the access to physio and home-use techniques? (Patients) / When should airways drainage techniques be started in patients with bronchiectasis and which one is the most effective and pragmatic? (Experts)*

Interventions aimed at promoting clearance of excess mucus are a mainstay of bronchiectasis management [1]. Although few studies have explored the impact of physiotherapy in bronchiectasis, airway clearance techniques seem to be safe and allow a better sputum expectoration with an increase in patients' quality of life [20]. Evidence on pulmonary rehabilitation is scarce; however, most of the studies demonstrated an increase in patients' performance and quality of life, and an increase of the time to the next exacerbation [21-23]. Both physicians and patients agreed that additional controlled trials of these interventions would be beneficial but that the priority may be in identifying methods that are accessible and that encourage adherence.

Consensus statement: Studies are required to optimize compliance and access to chest physiotherapy and pulmonary rehabilitation in bronchiectasis.

4. Identify patients at risk of poor outcomes (Patients) / What are the risk factors and causes for fast progression and poor outcomes in patients with bronchiectasis? (Experts)

Two scores have been recently proposed to predict adverse outcomes in bronchiectasis: the Bronchiectasis Severity Index (BSI) and the FACED score [4,24]. The BSI has been shown to accurately identify not only patients at risk of death, but also those with the highest risk of

complications, including exacerbations, hospitalization and impaired quality of life. Expert opinion suggests that disease severity may be useful as a framework for clinical decision allowing the appropriate targeting of therapies including long-term macrolides, inhaled antibiotic treatment and airway adjuncts [1]. An accurate assessment of prognosis is also essential for rational decisions regarding transplantation in bronchiectasis, and scoring may also be helpful in this context [25]. Several other factors need future multicentre, prospective, longitudinal studies to evaluate drivers of faster disease progression including the evaluation of microorganisms other than *P. aeruginosa*, microbiome parameters such as species diversity and richness, local and systemic inflammatory biomarkers and, other measurements of lung function impairment. The importance of comorbidities should also be explored as they may be amenable to treatment [26].

Consensus statements: 1) A deeper understanding of the inflammatory pathways in bronchiectasis is needed to develop new therapies. We recommend using emerging techniques and technologies (particularly proteomics, metabolomics and genomics) in large well-characterized cohorts to identify new treatment targets and deeper patient phenotyping; 2) An implementation study should be performed to demonstrate if the use of bronchiectasis severity scores could improve patient care.

Important research priorities identified by experts

1. When and how should Pseudomonas aeruginosa be eradicated in patients with bronchiectasis and does eradication result in improved outcomes?

Pseudomonas aeruginosa colonization defines a specific clinical phenotype of bronchiectasis and is associated with a 3-fold increase risk of death, a nearly 7-fold increase risk of hospital admissions, worse quality of life and more frequent exacerbations [27-29]. Evidence from CF suggests that attempts at eradication therapy targeting *Pseudomonas* can have success in converting patients to culture negative status [30]. Data in bronchiectasis and CF are of limited quality in defining both the early outcomes and long-term benefits. There are no large adequately powered studies to inform current practice, with most studies limited to observational case series [31,32]. Other studies using inhaled antibiotics therapies focused on treating those with persistent infection with the primary aim of reducing exacerbations [33]. An unexpected benefit seen in these trials is that they have consistently demonstrated small but significant rates of "eradication" of up to 10-15% [34]. Future randomized controlled studies will need clear definitions, techniques used and timing of testing for eradication.

Consensus statement: A randomized controlled trial of *Pseudomonas aeruginosa* eradication therapy, compared to no eradication treatment, should be performed.

2. What is the optimal antibiotic regimen (dosage, how many antibiotics, type, oral vs. intravenous vs. inhaled/nebulized, length of therapy) for an exacerbation of bronchiectasis?

Data evaluating the use of antibiotics during an exacerbation are extremely heterogeneous in terms of the antimicrobials used, route of administration, duration of treatment and clinical/microbiological endpoints. The possibility of treating exacerbations of bronchiectasis with nebulized antibiotics has also been tested in the past [35]. Notably, there are no randomized placebo-controlled trials of antibiotic regimes during exacerbation. The appropriate length of treatment for exacerbations is also unknown, while consensus guidelines recommend 14 days of treatment with antibiotic therapy [9]. The optimal duration of treatment is important as prolonged treatment carries a higher risk of driving antibiotic side effects, including resistance.

Consensus statements: 1) A randomized controlled trial comparing at least 14 days of antibiotic treatment for exacerbations with shorter course treatments is required.

3. What are the prevalence and characteristics of microbiological colonization, in patients with bronchiectasis across Europe (including bacteria, viruses, fungi, non-tuberculous mycobacteria and resistant microorganisms)?

H. influenzae and *P. aeruginosa* are the most commonly isolated organisms in several European studies using aerobic selective cultures, although no organisms are isolated in 23-27% of

patients [9,17,36,37]. New methods to study lung microbiota found that the diversity of airway infection is underestimated, with anaerobic bacteria found in up to 83% of sputum samples, and that three taxa, *Streptococcaceae*, *Pseudomonadaceae* and *Pasturellaceae* seem to be dominant [38]. However, most microbiome studies in bronchiectasis to date have been small, and therefore the clinical importance of this information is uncertain. Few data have been published regarding the prevalence of fungal colonization and it is now possible to perform sequencing of the fungal "mycobiome" in a similar way to that described above for bacteria[38-40]. The prevalence of non-tuberculous mycobacteria (NTM) in Europe is lower than 10%, although there seems to be a broad geographic variation [41]. The role of NTM between innocent colonizers or those causing chronic infection and the predisposing factors to this needs to be differentiated. There is also a paucity of data regarding the isolation of viruses and multi-resistant bacteria [4,18,29]. The EMBARC registry is currently collecting susceptibility patterns of bacteria causing chronic infection in patients with bronchiectasis patients and these data will be crucial in planning further interventional studies on antibiotics at European level [10]. Finally, it is desirable that agreed definitions of important concepts such as initial colonization, intermittent isolation, chronic colonization, chronic infection, eradication, and exacerbation should be adopted across Europe.

Consensus statements: 1) We suggest studies of the microbiome (incorporating bacteria and potentially fungi) in bronchiectasis linked to detailed clinical phenotyping data; 2) A longitudinal study of the bacteriology of bronchiectasis incorporating data on antibiotic resistance is needed.

4. What is the impact of long-term antibiotic therapy on microbial resistances?

The wide use of both systemic and inhaled antibiotics in patients with bronchiectasis causes rising concern about antimicrobial resistance, particularly for *P. aeruginosa* [42]. Since few options are currently available to intervene on microbial characteristics, most of the current efforts are dedicated to improve antibiotics characteristics and to optimize their administration [43]. Regarding the use of long-term antibiotics, periodic administration of rotating or fixed antibiotics is potentially associated with increased resistance and side effects, and risk of selection of fungal infection [38,44,45]. Although prolonged therapy with macrolides is effective in reducing exacerbations, there is a clear risk of antibiotic resistance for both sputum and oropharyngeal flora and a more careful selection of patients undergoing this treatment is recommended [46-49]. The risk of antimicrobial resistance to inhaled antibiotics seems to be very low despite prolonged and continuous administration, perhaps due to the high concentrations achieved in the airways [33].

Consensus statements: 1) Longitudinal studies should be conducted in patients receiving oral and inhaled antibiotics to monitor for the emergence of antibiotic resistance; 2) Studies should ideally evaluate whether cyclical or continuous administration of long-term antibiotics is superior both in terms of clinical efficacy and the emergence of resistance.

5. *When should a long-term suppressive antibiotic therapy (either oral or inhaled/nebulized) be started in patients with bronchiectasis (according to the presence or not of P. aeruginosa or other pathogens) and what should be the endpoints for efficacy?*

Several reports describe the long-term use of inhaled antibiotics in about 10% and of macrolides in about 30% of all bronchiectasis patients [50-52]. Various inhaled antibiotics have been tested to reduce bacterial load from bronchiectasis patients' airways and related symptoms and exacerbations such as tobramycin [53,54], colistin [55], gentamicin [56], and aztreonam [57]. In bronchiectasis data on inhaled antibiotics are limited and results have been mixed, with tolerability being one of the major issues. As a result of the challenges in published trials, none are as yet licensed for use in bronchiectasis by authorities in Europe or the United States.

Three different trials have largely demonstrated the usefulness of long-term macrolides in reducing the number of exacerbations with consequent improvement of quality of life and in some cases with slower lung function decline [46-48]. Nevertheless, it is important to remember several concerns about long-term use of macrolides, including antimicrobial resistance [48,58], the potential to promote macrolide-resistant NTM [59-61] and an increased risk of cardiovascular complications [62]. It seems that macrolides are clearly beneficial in patients with bronchiectasis, but the optimal patient population to benefit has not been defined. The inclusion criteria of the trials were broad and each trial used a different regimen. Trials had either 6-month [46] or 12-month [47,48] treatment duration and the long-term safety and resistance impact of these drugs is unknown.

Consensus statements: 1) Further studies are required to define the optimal patient population to benefit from long-term macrolide therapy; 2) More "real world" data on the long-term safety and resistance impact of macrolide treatment are required; 3) Inhaled antibiotics such as colistin and gentamicin should be subject to definitive phase III trials to demonstrate a reduction in exacerbations and improvements in quality of life.

6. What are the key factors leading to P. aeruginosa colonization?

The reason why some patients with bronchiectasis become colonized with *P. aeruginosa* while the majority do not is unexplained. Genetic studies may identify host risk factors for *P. aeruginosa* colonization, and a modest effect of mannose binding lectin polymorphisms on susceptibility has been shown in both bronchiectasis and CF [63,64]. Microbial factors are also important in *P. aeruginosa* colonization, with person-person transmission and epidemic strains being well described in CF but in non-CF bronchiectasis [65]. Furthermore, different *P. aeruginosa* strains in CF have been recognized to have variation in *in vitro* phenotypes that appear to translate into clinically meaningful outcomes [66,67].

Consensus statements: 1) Mechanistic studies investigating the genetic, microbiological, inflammatory and clinical susceptibility factors for *P. aeruginosa* colonization should be conducted; 2) Long-term cohort studies are needed to identify which patients acquire *P. aeruginosa* colonization and to identify its independent effects on outcome.

7. What are the indications of oral versus inhaled/nebulized long-term suppressive antibiotic treatment?

There are no head to head trials of oral *versus* inhaled antibiotics. The criteria to choose between oral macrolides and inhaled antibiotics are still not clear and the decision is still empirical and based on personal experience and local healthcare prescription rules. Nevertheless it is clear that some factors could justify the antibiotic choice such as the presence of specific antibiotic allergies and side effects, the patients' preferences and ability to manage inhalations, the co-existence of rhinosinusitis and cardiovascular comorbidities. In the absence of head to head trials, large registries should provide important information about treatment patterns [10]. In addition, ongoing randomized trials of inhaled antibiotics which include macrolide-treated patients will evaluate the important question of whether inhaled antibiotics can provide added benefit.

Consensus statement: Comparative studies are needed to determine the optimal choice between oral and inhaled antibiotic treatment in patients with and without *P. aeruginosa* colonization.

8. What are the best molecule, dose, regimen and duration for long-term oral antibiotic therapy in patients with bronchiectasis (according to the presence or not of Pseudomonas aeruginosa or other pathogens)?

Three major studies recently demonstrated the efficacy of long-term macrolides in bronchiectasis in double-blind randomized trials [46-48]. Key questions remain regarding oral antibiotic therapy including: Do macrolides have to be continued lifelong, or can they be withdrawn e.g. after 12 months? The most appropriate dose and macrolide agent to minimise side effects and development of antimicrobial resistance has not been determined. It is not known if alternative oral antibiotic agents such as tetracyclines or beta-lactams are equally effective when given long-term. As the maximum duration of macrolide treatment was 12 months, it is not known if the effectiveness of macrolides wanes over time as antibiotic resistance develops or if effectiveness is sustained.

Consensus statement: Randomized controlled trials should address whether alternative long-term oral antibiotics (other than macrolides) are effective at reducing exacerbations.

Important research priorities identified by patients

Other important themes have been identified from the top ranking patient priorities with a special attention focused on condition management, communication and information. These areas were all strongly supported by the expert working group.

1. Condition management

The questionnaire identified a number of research topics that could help improve the management of their bronchiectasis. Over 96% of respondents felt that their bronchiectasis could be better managed through having a self-management plan co-designed with their HCP, and access to physiotherapy/pulmonary rehabilitation, which also includes teaching them how to use techniques/equipment at home [1,22,40,68,69]. Self-management plans facilitated by good communication between patients and HCPs empower patients to manage and cope with their condition more confidently and independently [70,71]. An important component of these self-management strategies, and in reducing hospitalization, is the awareness of HCPs' of bronchiectasis and available and appropriate community care and physiotherapy services [1,68,72].

Consensus statement: Studies should be conducted to determine the effectiveness of patient self-management in bronchiectasis and adherence to treatment.

2. Communication and information

One of the top priorities for patients was good communication between HCPs and each patient. Patients also highly ranked the need for access to reliable plain language information on living with bronchiectasis [70]. This shows that patients' do not feel their information needs are being met, as they are struggling to find accurate information to help them live with their condition, which is a role that can be supported by the clear communication of information to patients by HCPs, both at the point of diagnosis and as their condition/needs change [70]. Increasingly patients look to the internet for information on their condition; therefore healthcare professionals can provide an invaluable service by signposting patients and their carers/families to reliable plain language information both online and in paper format i.e. medically accurate, plain language information leaflets. This role can be especially important for people with bronchiectasis and other neglected and under-resourced conditions, where there is less public and healthcare professional awareness and few widely available multilingual information leaflets, patient organisations and support groups. The potential for enhanced information packages or patient alert systems to help adherence and self-management offers a potentially cost effective solution acceptable to patients, with examples available in other disease areas and with patients involved in the development of resources.

Consensus statements: 1) Further research with patients as partners could explore the specific information needs of bronchiectasis patients, effective HCP and patient communication strategies, and develop improved patient-reported outcomes; 2) A

multidisciplinary education programme is needed for bronchiectasis to increase awareness among non-specialists in secondary care and among primary care.

Priorities identified in this document should be important to inform the work of individual researchers, the EMBARC network as a whole, charities, funding bodies, regulators and healthcare policy makers. The EMBARC steering committee and the international advisory board (www.bronchiectasis.eu) unanimously approved the present document and research priorities with the aim of supporting studies designed to answer these questions.

A key finding of our consensus process is that very few of our research questions can be answered by pure basic or clinical research and almost all of these priorities require an integrated approach with careful clinical phenotyping, as will be available in multinational registries, linked to translational and mechanistic research. It is well recognized that there is a barrier between basic and clinical researchers leading to a "translation gap". As a result of this process, we propose that a key objective of the EMBARC Clinical Research Collaboration should be to promote collaboration between clinical and scientific researchers in the field of bronchiectasis.

Our selection of the most important research priorities herein does not imply that other research questions are not also important. All of the 55 priorities identified by the Delphi process and all of the priorities assessed by patients were rated as important by the majority of questionnaires. Furthermore, patients reported different priorities specifically based on their daily experience of and concerns about the future of their bronchiectasis. This does not

preclude that other signs/symptoms, such as weight loss or depression, are not crucial with a relevant impact on outcomes.

One of the limitations of this project for the patients' questionnaire is that we used pre-worded and multiple-choice questions, rather than running one-to-one interviews or focus groups, potentially missing the complexity of bronchiectasis patients' experiences. However, our questionnaire seems to be the best method to rapidly reach the largest sample size of patients with bronchiectasis across Europe expressing the patients' perspective on "knowledge gaps" and it is the largest such endeavour published so far. Another limitation is the absence of the involvement among experts (mainly physicians running bronchiectasis clinics) of other HCPs taking care of bronchiectasis patients, such as general practitioners. Their presence would have led to a change in research priorities, probably in favour of non-antibiotic treatments. Finally, we should acknowledge that 40% of respondents to the patient questionnaires were people from the UK and this finding could slightly affect the generalizability of patients' priorities across Europe. However, the pragmatic methodology we used in this project facilitated insight into an under-researched population, especially in terms of patient-reported needs, and a health issue that affects patients and services across Europe. Although response rates differed for language/country and disease, we should recognize that the sample did share key characteristics with the European respiratory patient population.

One of the strengths of this document is the comparison, for the first time in literature, of both experts' and patients' perspectives in bronchiectasis research in order to point out their shared research priorities. Furthermore, the voting process for both experts and patients was performed anonymously.

CONCLUSIONS

This consensus statement identifies the key research priorities as determined by physicians caring for bronchiectasis patients, and by the patients themselves and the friends and family helping care for them. This document will be a valuable resource for public and private stakeholders involved in designing calls for research funding at both national and international level. The EMBARC initiative seeks to stimulate clinical and translational research in bronchiectasis and the priorities identified here provide the clearest possible roadmap towards improving our understanding of the disease and the quality of care for bronchiectasis patients.

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TABLES

Table 1. Ranking of experts' research priorities in bronchiectasis

	Research Question	Area of research	Score
1	When and how (molecule, dose, regimen, route - intravenous, oral, inhaled/nebulized- and duration) should Pseudomonas aeruginosa be eradicated in patients with bronchiectasis and do their outcomes improve after that?	Acute and long-term suppressive antibiotic therapy	4.35 / 5
2	What are the indications and what is the optimal antibiotic therapy (dosage, how many antibiotics, type, oral vs. intravenous vs. inhaled/nebulized, length of therapy) for an exacerbation of bronchiectasis	Exacerbation	4.30 / 5
3	What are the prevalence and characteristics of microbiological colonization, chronic and acute infections (exacerbations and pneumonia) in patients with bronchiectasis across Europe (including bacteria, viruses, fungi, non-tuberculous mycobacteria and resistant microorganisms)?	Epidemiology	4.29 / 5

4	What are the risk factors and causes for fast progression and poor outcomes (e.g.: hospitalization, lung transplantation and mortality) in patients with bronchiectasis?	Outcomes, prognosis and healthcare utilization	4.28 / 5
5	What is the impact of long-term antibiotic therapy on microbial resistances?	Acute and long-term suppressive antibiotic therapy	4.21 / 5
6	When should a long-term suppressive antibiotic therapy (either oral or inhaled/nebulized) be started in patients with bronchiectasis (according to the presence or not of Pseudomonas aeruginosa or other pathogens) and what would be endpoints for efficacy?	Acute and long-term suppressive antibiotic therapy	4.20 / 5
7	What are the key factors leading to Pseudomonas aeruginosa colonization?	Microbiology and microbial diagnostics	4.16 / 5
8	What are the indications of oral versus inhaled/nebulized long-term suppressive antibiotic treatment?	Acute and long-term suppressive antibiotic therapy	4.12 / 5
9	What are the best molecule, dose, regimen and duration for long-term oral antibiotic therapy in patients with bronchiectasis (according to the presence or not of	Acute and long-term suppressive antibiotic therapy	4.11 / 5

	Pseudomonas aeruginosa or other pathogens)?		
10	What are the causes of an exacerbation of bronchiectasis?	Exacerbation	4.09 / 5
11	When and how (molecule, dose, regimen, route - intravenous, oral, inhaled/nebulized- and duration) should pathogens other than Pseudomonas aeruginosa be eradicated in patients with bronchiectasis and do their outcomes improve after that?	Acute and long-term suppressive antibiotic therapy	4.08 / 5
12	What are the best molecule, dose, regimen and duration for long-term inhaled/nebulized antibiotic therapy in patients with bronchiectasis (according to the presence or not of Pseudomonas aeruginosa or other pathogens)?	Acute and long-term suppressive antibiotic therapy	4.08 / 5
13	What are the baseline investigations to evaluate etiologies in patients with bronchiectasis?	Etiology, radiology and pulmonary function tests	4.08 / 5
14	Do different etiologies of bronchiectasis predetermine microbiological characteristics and affect severity, patients' quality of life and disease progression in patients with bronchiectasis?	Etiology, radiology and pulmonary function tests	4.00 / 5
15	How to assess the severity of an exacerbation of	Exacerbation	3.98 / 5

	bronchiectasis and what is its impact on long-term outcomes?		
16	When should airways drainage techniques be started in patients with bronchiectasis and which one is the most effective and pragmatic?	Physiotherapy and pulmonary rehabilitation	3.97 / 5
17	Which is the most useful severity score in clinical practice in patients with bronchiectasis?	Outcomes, prognosis and healthcare utilization	3.96 / 5
18	Does an early referral to a specialist clinic change outcomes in patients with bronchiectasis?	Outcomes, prognosis and healthcare utilization	3.96 / 5
19	What is the average lung function decline in patients with bronchiectasis across Europe and what are risk or protective factors for that?	Etiology, radiology and pulmonary function tests	3.93 / 5
20	Which factors, including etiology of bronchiectasis, patients' characteristics or bacteria isolated in sputum, affect macrolide efficacy in patients with bronchiectasis?	Acute and long-term suppressive antibiotic therapy	3.92 / 5
21	What are the characteristics of patients' microbiome both during stable state and exacerbation and what is its impact on severity of the disease and follow-up?	Microbiology and microbial diagnostics	3.90 / 5

22	What is the role of viruses, atypicals, fungi and anaerobes (both single and in co-infection) in patients with bronchiectasis during both stable state and exacerbation and what is their impact of patients' severity and outcomes?	Microbiology and microbial diagnostics	3.89 / 5
23	What is the prevalence of different etiologies of bronchiectasis across Europe?	Epidemiology	3.87 / 5
24	Are influenza and/or pneumococcal vaccines and other immunotherapies effective in preventing exacerbations in patients with bronchiectasis?	Other	3.84 / 5
25	What are the adverse events of a both oral and inhaled/nebulized suppressive antibiotic therapy in patients with bronchiectasis?	Acute and long-term suppressive antibiotic therapy	3.83 / 5
26	What are the prevalence and type of long-term suppressive oral (macrolide and non-macrolide) and nebulized/inhaled antibiotic therapy in patients with bronchiectasis across Europe?	Epidemiology	3.83 / 5
27	When should pulmonary rehabilitation be started in patients with bronchiectasis and what is its impact on patients' outcomes?	Physiotherapy and pulmonary rehabilitation	3.82 / 5

28	What are incidence, prevalence, patients' demographic characteristics and comorbidities of bronchiectasis across Europe?	Epidemiology	3.81 / 5
29	Is airway clearance useful during an acute exacerbation of bronchiectasis?	Exacerbation	3.80 / 5
30	Should we establish new breakpoints for predicting bacteria susceptibility when inhaled/nebulized antibiotics are used?	Microbiology and microbial diagnostics	3.78 / 5
31	What are the indications/contraindications for lung transplantation in bronchiectasis and what are patients' outcomes after lung transplantation?	Other	3.73 / 5
32	Which are the best systemic (e.g. blood) or local (e.g. sputum) inflammatory markers for the diagnosis, management and follow-up of patients with bronchiectasis?	Pathogenesis and mechanisms of the disease	3.73 / 5
33	What is the distribution of inhaled/nebulized antibiotics with different formulations and devices in lungs with bronchiectasis?	Acute and long-term suppressive antibiotic therapy	3.73 / 5
34	Do specific patient education packages, self-management plans and patients support groups improve outcomes in	Other	3.72 / 5

	patients with bronchiectasis?		
35	Where are patients with bronchiectasis managed across Europe, including specialistic (bronchiectasis) clinics, cystic fibrosis centers/clinics, respiratory clinics or general practitioners?	Epidemiology	3.67 / 5
36	Are other functional tests such as carbon monoxide diffusing capacity, six-minute walk test, lung clearance index, endurance shuttle walk, incremental exercise tests or accelerometers, markers for severity of the disease, outcomes and end-point for clinic	Etiology, radiology and pulmonary function tests	3.64 / 5
37	What is the best approach/score to evaluate radiological severity in patients with bronchiectasis?	Etiology, radiology and pulmonary function tests	3.63 / 5
38	May cross-infection occur in patients with bronchiectasis and is patients' segregation required?	Microbiology and microbial diagnostics	3.62 / 5
39	What are the healthcare costs of bronchiectasis management across Europe?	Epidemiology	3.60 / 5
40	What is the role of inhaled hyperosmolaric therapy (e.g. ialuronate, mannitol, NaCl 3%, 6%, 7%, etc.)?	Non Antibiotic and anti-inflammatory therapies	3.53 / 5

41	What are the radiological changes on bronchiectasis over time?	Etiology, radiology and pulmonary function tests	3.52 / 5
42	What is the impact of haemoptysis on prognosis of patients with bronchiectasis and how should it be managed?	Other	3.51 / 5
43	What are the genetic and epigenetic findings in patients with bronchiectasis compared to healthy controls and what is their role in acquisition of specific pathogens and patients' outcomes?	Pathogenesis and mechanisms of the disease	3.50 / 5
44	What are the characteristics and outcomes of patients with bronchiectasis undergoing surgery, including segmentectomy, lobectomy or pneumonectomy?	Other	3.49 / 5
45	What is the role of systemic steroids during an exacerbation of bronchiectasis?	Exacerbation	3.47 / 5
46	Is there an increased rate of innate immune defects (e.g., Mannose-binding lectin deficiency, common variable immunodeficiency, IgM or IgA deficiency, complement deficiency etc.) in specific patients with bronchiectasis?	Pathogenesis and mechanisms of the disease	3.46 / 5
47	What is the role of long-term inhaled corticosteroids in	Non Antibiotic and	3.38 / 5

	patients with bronchiectasis?	anti-inflammatory therapies	
48	What are the frequency of cystic fibrosis (CF) heterozygosity and the role of CFTR and ENaC dysfunction in patients with bronchiectasis?	Pathogenesis and mechanisms of the disease	3.36 / 5
49	What is the role of oral mucolytics in patients with bronchiectasis?	Non Antibiotic and anti-inflammatory therapies	3.35 / 5
50	What is the role of anti-proteinases/elastase inhibitors in patients with bronchiectasis?	Non Antibiotic and anti-inflammatory therapies	3.19 / 5
51	What is the role of systemic anti-inflammatory therapies (such as steroids or non-steroidal anti-inflammatory drugs) during stable state in patients with bronchiectasis?	Non Antibiotic and anti-inflammatory therapies	3.15 / 5
52	What is the role of protease-antiprotease imbalance, matrix metalloproteinase and neuron-specific enolase in patients with bronchiectasis?	Pathogenesis and mechanisms of the disease	3.14 / 5
53	What is the role of anticholinergic therapy in patients with bronchiectasis?	Non Antibiotic and anti-inflammatory therapies	3.12 / 5

54	What is the role of phosphodiesterase type 4 inhibitors in patients with bronchiectasis?	Non Antibiotic and anti-inflammatory therapies	2.97 / 5
55	Does daily proton-pump inhibitor use impact clinical outcomes in patients with bronchiectasis?	Non Antibiotic and anti-inflammatory therapies	2.96 / 5

Table 2: Ranking of patients' and carers' research priorities in bronchiectasis

	Research Question	Area of research
1	How does bronchiectasis develop and continue?	How bronchiectasis is managed by doctors
2	How can communication between healthcare professionals and each patient be optimised to improve self-management?	Self-management by patients
3	What makes some patients get worse?	How bronchiectasis is managed by doctors
4	What are causes of bronchiectasis?	How bronchiectasis is managed by doctors
5	What are the triggers for an exacerbation?	How bronchiectasis is managed by doctors
6	How can self-management programmes and care plans designed with each person be most effective in helping patients have greater control over their condition and recognise/manage an exacerbation?	Self-management by patients
7	How can physiotherapy be accessible to all patients, and teach them to use the techniques and how to use the equipment at home effectively?	Self-management by patients
8	How can reliable, plain language information on living with	Self-management by

	bronchiectasis be accessible to patients?	patients
9	How can patients at increased risk of poor outcomes or needing urgent treatment be identified?	How each person's bronchiectasis is monitored
10	How can awareness of bronchiectasis in community care services be improved, e.g. among community-based nurses and physiotherapists	How bronchiectasis is treated
11	Are there ways to diagnose bronchiectasis earlier?	How bronchiectasis is managed by doctors
12	How can awareness of the role of physiotherapy and pulmonary rehabilitation in treating bronchiectasis be improved?	How bronchiectasis is treated
13	Can we testing new techniques for managing bronchiectasis in real world environments, such as at home and community settings (not in the laboratory or in hospitals) to improve how bronchiectasis is managed?	How bronchiectasis is managed by doctors
14	Is there a link between getting a cold and exacerbation?	How bronchiectasis is managed by doctors
15	Can regular lung function testing help notice changes or increased risk of an exacerbation?	How each person's bronchiectasis is monitored

16	Is there a relationship between bronchiectasis and other conditions, such as asthma, 'acid' reflux, and inflammatory bowel diseases?	How bronchiectasis is managed by doctors
17	Can new medicines that can be taken in new ways be developed e.g. inhaled or nebulised	How bronchiectasis is treated
18	Can regular sputum examinations when a person is stable and during exacerbation help us learn more about how the condition changes?	How each person's bronchiectasis is monitored
19	Can we develop better ways of teaching people to use their medicines?	How bronchiectasis is treated
20	Can we provide and will providing test results help each patient follow their progress?	Self-management by patients
21	How can primary care doctors be educated to prescribe the same dose/ length of antibiotic therapy for exacerbations in bronchiectasis as used in CF?	How bronchiectasis is treated
22	Can vaccines be developed/ used to prevent exacerbations?	How bronchiectasis is treated
23	How often/why bronchiectasis occurs in certain groups of people?	How bronchiectasis is managed by doctors
24	How can we ensure that each person has access to a home IV antibiotic service to avoid unnecessary hospital	Self-management by patients

	admissions?	
25	How can awareness and use of peer support forums and social media to exchange information be raised?	Self-management by patients
26	How can patients have and use equipment at home to monitor their symptoms?	How each person's bronchiectasis is monitored
27	How can the monitoring and treatment of coughing up blood be achieved?	How each person's bronchiectasis is monitored
28	Can using longer-term antibiotic therapy when a person's condition is stable improve treatment?	How bronchiectasis is treated
29	Can having regular computed tomography scans to look for changes and increased risk of an exacerbation improve monitoring?	How each person's bronchiectasis is monitored

FIGURE LEGENDS

Figure 1. Processes to define both experts' and patients' research priorities in bronchiectasis.

Figure 2. a) Aspects of bronchiectasis found either difficult or very difficult by patients (n = percentage of respondents); b) Aspects of bronchiectasis found difficult or very difficult by patients in comparison with the percentage of patients who identified the same aspects as 'not an issue' (n = percentage of respondents).